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(64) Pharmaceutical formulations of acid labile substances for oral use.

(57) Pharmaceutical preparation containing an acid labile compound together with an alkaline reacting compound or an alkaline salt of an acid labile compound optionally together with an alkaline compound as the core material, one or more subcoating layers comprising inert reacting compounds which are soluble or rapidly disintegrating in water, or polymeric, water soluble filmforming compounds, optionally containing pH-buffering alkaline compounds and an enteric coating as well as a process for the preparation thereof and the use in the treatment of gastrointestinal diseases.

**EP 0 244 380 A2**

## Pharmaceutical formulations of acid labile substances for oral use

### Field of the Invention

The present invention is related to new pharmaceutical preparations containing acid labile substances for oral use, to a method for the manufacture of such preparations and to a method of affecting gastric acid secretion and providing gastrointestinal cytoprotective effect when using them.

### Background of the Invention

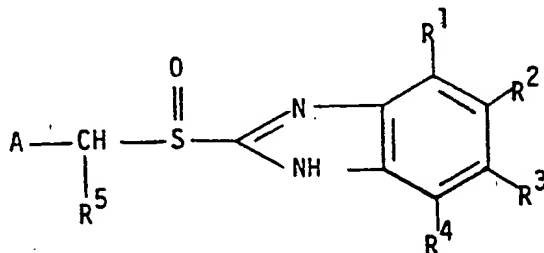
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Acid labile substances present a problem to the formulator when formulating a pharmaceutical dosage form for oral use. In order to prevent the substances from contact with the acid reacting gastric juice after oral intake, the conventional way to solve this problem is to coat the dosage form with an enteric coating. The coating is a group of substances/polymers with the common feature of being practically insoluble in acid media, while they are soluble in neutral to alkaline media. For substances that are labile in acid media, but have better stability in neutral to alkaline media, it is often advantageous to add alkaline reacting inactive constituents in order to increase the stability of the active compound during manufacture and storage.

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A group of compounds exerting these stability properties are substituted benzimidazoles with the general formula I

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wherein A is an optionally substituted heterocyclic group and R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, and R<sup>4</sup> are the same or different as defined below and R<sup>5</sup> is H or a lower alkyl, or the compound 2-[(2-dimethylamino-benzyl)sulfinyl]-benzimidazole.

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The compounds with the general formula I are virtually biologically inactive as such, but degrade/transform to active inhibitors of certain enzyme systems in acid media.

- 5 As examples of compounds with the mentioned properties the compounds described in the patents US-A-4045 563, EP-B1-0 005 129 and BE-898 880 and the patent applications EP-85850258,6, EP-A1-0 080 602, EP-0127 736, EP-0 134 400, EP-0 130 729, EP-0 150 586, DE-3415971 GB-2 082 580 and SE-A-8504048-3 may be mentioned. The last application describes
- 10 2- (2-disubstituted-aminobenzyl)sulfinyl benzimidazoles, e.g. 2- (2-di-methylaminobenzyl)sulfinyl benzimidazole, also called, NC-1300 and presented by Prof. S. Okabe at the Symposium on Drug Activity held on Oct 17th 1985 in Nagoya, Japan, and which interacts with the  $H^+K^+$ -ATPase after acid degradation within the parietal cells. (See for instance B.
- 15 Wallmark, A. Brändström and H. Larsson "Evidence for acid-induced transformation of omeprazole into an active inhibitor of  $H^+K^+$ -ATPase within the parietal cell", Biochemica et Biophysica Acta 778, 549-558, 1984). Other compounds with similar properties are further mentioned in the patent US-4 182 766 and the patent applications GB-2 141 429, EP-0
- 20 146 370 and GB-2 082 580. A common feature of these compounds are that they are transformed into the biologically active compounds via rapid degradation/transformation in acid media.

The stability profile of some compounds with the general formula I above

25 is exemplified in the Table 1 below, where the half-life of the degradation/transformation reaction in solution at pH 2 and 7 are given.

Table 1. Rate of degradation/transformation of compounds  
with the general structure

5

$$A-CH_2-S(=O)-\begin{array}{c} \text{N} \\ \diagup \\ \text{C} \\ \diagdown \\ \text{N} \\ | \\ \text{H} \end{array} \begin{array}{c} \text{R}^2 \\ \text{R}^3 \end{array}$$

Compound No	A	R <sup>2</sup> R <sup>3</sup>	Half-life (minutes) for the transformation to the active moiety	
			at pH = 2	at pH = 7
1.		5-COOCH <sub>3</sub> ; 6-CH <sub>3</sub>	11	150
2.		5-CH <sub>3</sub> ; H	5.4	1700
3.		5-CF <sub>3</sub> ; H	1.9	122
4.		5-CF <sub>3</sub> ; H	2.0	8.8
5.		5-OCH <sub>3</sub> ; H	3.7	1620

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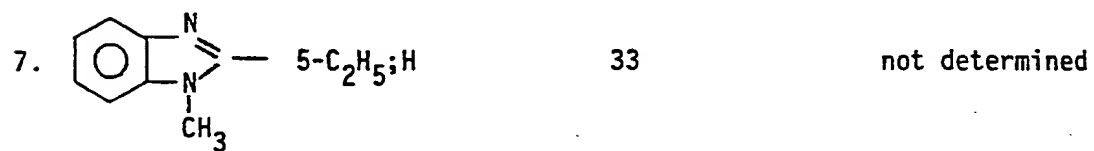
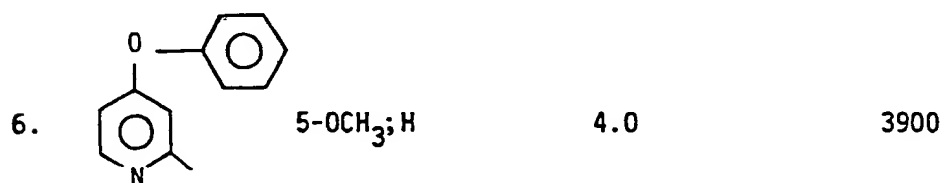
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Cont.

Compound No	Half-life (minutes) for the transformation to the active moiety	
	A	$R^2$ $R^3$ at pH = 2 at pH = 7



Substituted sulfoxides, such as for instance the substituted benzimidazoles described in EP-B1-0005129 are potent inhibitors of gastric acid secretion. The substituted benzimidazoles are susceptible to degradation/transformation in acid reacting and neutral media.

5

It is an inherent property of these compounds to be activated to the active moiety in the acid environment within the parietal cells. The activated compound interacts with the enzyme in the parietal cells, which mediates the production of hydrochloric acid in the gastric mucosa. All compounds of the class of substituted benzimidazoles, containing a sulfoxide grouping, which interferes with the  $H^+K^+-ATPase$  in the parietal cells hitherto known are all also degraded in acid media.

- 15 A pharmaceutical dosage form of acid labile substances, which prevents the substances from contact with acidic gastric juice, must be enteric coated. Ordinary enteric coatings, however, are made of acidic compounds. If covered with such a conventional enteric coating, the acid labile substance rapidly decomposes by direct or indirect contact with it, with the result that the preparations become badly discoloured and lose in content of the active compound with the passage of time.

- In order to enhance the storage stability, the cores which contain the acid labile substance must also contain alkaline reacting constituents.
- 25 When such an alkaline core is enteric coated with an amount of a conventional enteric coating polymer such as, for example, cellulose acetate phthalate, that permits the dissolution of the coating and the active drug contained in the cores in the proximal part of the small intestine, it also will allow some diffusion of water or gastric juice through the enteric coating into the cores, during the time the dosage form resides in the stomach before it is emptied into the small intestine. The diffused water or gastric juice will dissolve parts of the core in the close proximity of the enteric coating layer and there form an alkaline solution inside the coated dosage form. The alkaline solution will interfere with the enteric coating and eventually dissolve it.
- 35

In DE-A1-3 046 559 a way to coat a dosage form is described. First the dosage form is coated with a water insoluble layer containing microcrystalline cellulose and then with a second enteric coating with the aim to achieve a dosage form which releases the active drug in the colon. This method of preparation will not give the desired release of the compounds with the general formula I above in the small intestine.

US-A-2 540 979 describes an enteric coated oral dosage form, where the enteric coating is combined with a second and/or first coating of a water insoluble "wax" layer. This method of preparation is not applicable on cores containing a compound with the general formula I since direct contact between substances such as cellulose acetate phthalate (CAP) and a compound of formula I causes degradation and discolouration of the compounds of the formula I.

DE-B2-23 36 218 describes a method to produce a dialysis membrane consisting of a mixture of one or more conventional enteric coating polymers and one or more insoluble cellulose derivatives. Such a membrane will not give a proper protection of the acid labile compounds of the formula I in gastric juice.

DE-A1-1 204 363 describes a three-layer coating procedure. The first layer is soluble in gastric but is insoluble in intestinal juice. The second is water soluble regardless of pH and the third layer is an enteric coating. This preparation as well as the preparation described in DE-A1-1 617 615 result in a dosage form which is not dissolved in gastric juice and which only dissolves slowly in intestinal juice. Such preparations cannot be used for the compounds of the formula I, where a rapid release of the drug in the small intestine is needed. DE-A1 12 04 363 describes coating with three layers to achieve release of a drug in the ileum, an aim which is outside the scope of the present invention. GB-A-1 485 676 describes a way to obtain a preparation which effervesces in the small intestine. This is obtained by the enteric coating of a core containing the active drug and an effervescing system such as a

combination of carbonate and/or bicarbonate salt and a pharmaceutically acceptable acid. This formulation cannot be adopted for a pharmaceutical dosage form containing a compound of formula I as the presence of an acid in contact with a compound of formula I in the cores would give as  
5 a result that the compound of formula I was degraded.

WO 85/03436 describes a pharmaceutical preparation, wherein cores containing active drugs mixed with for instance buffering components such as sodium dihydrogenphosphate with the aim of maintaining a  
10 constant pH and a constant rate of diffusion, are coated with a first coating which controls the diffusion. This formulation cannot be adopted for acid labile compounds where a rapid release in the small intestine is wanted. Direct application of an enteric coating onto the cores would also adversely influence the storage stability of such dosage forms  
15 containing acid labile compounds.

#### Outline of the invention

According to the present invention it has been found that the known acid  
20 labile compounds with the general formula I above in which  $R^1$ ,  $R^2$ ,  $R^3$  and  $R^4$  are the same or different and are



- (a) hydrogen
  - (b) halogen, e.g. F, Cl, Br, I
  - (c) -CN
  - (d) -CHO
  - (e) -CF<sub>3</sub>
  - (f)  $\begin{array}{c} \text{O} \\ \parallel \\ -\text{C}-\text{R}^{11} \end{array}$
  - (g) -O-C-R<sup>12</sup>
  - (h) -CH(OR<sup>13</sup>)<sub>2</sub>
  - (i) -(Z)<sub>n</sub>-B-D
  - (j) aryl containing up to 10 carbon atoms
  - (k) aryloxy containing up to 10 carbon atoms, optionally substituted by alkyl containing 1-6 carbon atoms
  - (l) -alkylthio containing 1-6 carbon atoms
  - (m) -NO<sub>2</sub>
  - (n) -alkylsulfinyl containing 1-6 carbon atoms
  - (o) or wherein adjacent groups R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> together with the adjacent carbon atoms in the benzimidazole ring form a 5-, 6- or 7-membered monocyclic ring or a 9-, 10- or 11-membered bicyclic ring, which rings may be saturated or unsaturated and may contain 0-3 hetero atoms selected from -N- and -O-, and which rings may be optionally substituted with 1-4 substituents selected from alkyl groups with 1-3 carbon atoms, alkylene radicals containing 4-5 carbon atoms giving spiro compounds, or two or four of these substituents together form one or two oxo groups
- $\begin{array}{c} \text{O} \\ \parallel \\ (-\text{C}-), \text{whereby if } \text{R}^1 \text{ and } \text{R}^2, \text{R}^2 \text{ and } \text{R}^3 \text{ or } \text{R}^3 \text{ and} \end{array}$

$R^4$  together with the adjacent carbon atoms in the benzimidazole ring form two rings they may be condensed with each other, in which formulas  $R^{11}$  and  $R^{12}$ , which are the same or different, are

5

10

15

20

 $R^{13}$  is

25 Z is

n is

B is

30

- (a) aryl containing up to 10 carbon atoms
- (b) alkoxy containing 1-4 carbon atoms
- (c) alkoxyalkoxy containing 1-3 carbon atoms in each alkoxy part
- (d) arylalkoxy containing 1-2 carbon atoms in the alkoxy part and up to 10 carbon atoms in the aryl part
- (e) aryloxy containing up to 10 carbon atoms
- (f) dialkylamino containing 1-3 carbon atoms in the alkyl parts, or
- (g) pyrrolidino or piperidino, optionally substituted with alkyl containing 1-3 carbon atoms;

- (a) alkyl containing 1-4 carbon atoms, or
- (b) alkylene containing 2-3 carbon atoms;

-O- or  $\begin{array}{c} \text{O} \\ || \\ -\text{C}- \end{array}$  ;

0 or 1;

- (a) alkylene containing 1-6 carbon atoms
- (b) cycloalkylene containing 3-6 carbon atoms

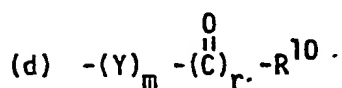
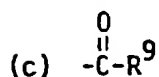
- (c) alkenylene containing 2-6 carbon atoms
- (d) cycloalkylene containing 3-6 carbon atoms,  
or
- (e) alkynylene containing 2-6 carbon atoms;

5

D is

- (a) H
- (b) -CN

10



wherein

15  $R^9$  is

- (a) alkoxy containing 1-5 carbon atoms, or
- (b) dialkylamino containing 1-3 carbon atoms in  
the alkyl parts;

m is

0 or 1;

20

r is

0 or 1;

Y is

- (a) -O-
- (b) -NH-
- (c) -NR<sup>10</sup>-;

25

 $R^{10}$  is

- (a) H
- (b) alkyl containing 1-3 carbon atoms
- (c) arylalkyl containing 1-2 carbon atoms in the  
alkyl part and up to 10 carbon atoms in the  
aryl part

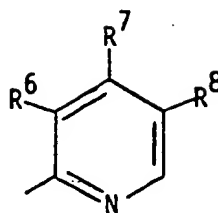
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(d) aryl containing up to 10 carbon atoms;

$R^5$  is

H,  $CH_3$  or  $C_2H_5$ ;

5 A is especially a pyridyl group  
in which  $R^6$  and  $R^8$  are the same  
or different, are



10

(a) H or

(b) alkyl containing 1-6 carbon atoms;

$R^7$  is

15

(a) H

(b) alkyl containing 1-8 carbon atoms

(c) alkoxy containing 1-8 carbon atoms

(d) alkenyloxy containing 2-5 carbon atoms

(e) alkynyloxy containing 2-5 carbon atoms

(f) alkoxyalkoxy containing 1-2 carbon atoms in  
each alkoxy group

20

(g) aryl containing up to 10 carbon atoms

(h) arylalkyl containing 1-6 carbon atoms in the  
alkyl part and up to 10 carbon atoms in the aryl  
part

25

(i) aryloxy containing up to 10 carbon atoms,  
optionally substituted by alkyl containing 1-6  
carbon atoms

(j) arylalkoxy containing 1-6 carbon atoms in the  
alkoxy part and up to 10 carbon atoms in the  
aryl part

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(k) dialkylaminoalkoxy containing 1-2 carbon atoms  
in the alkyl substituents on the amino nitrogen  
and 1-4 carbon atoms in the alkoxy group

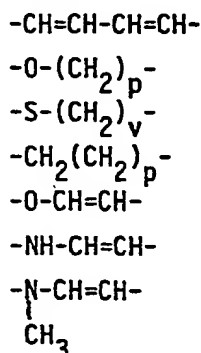
(l) oxacycloalkyl containing one oxygen atom and 3-7  
carbon atoms

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(m) oxacycloalkoxy containing two oxygen atoms and  
4-7 carbon atoms

(n) oxacycloalkylalkyl containing one oxygen atom  
and 4-7 carbon atoms

- (o) oxacycloalkylalkoxy containing two oxygen atoms and 4-6 carbon atoms, or  
 (p)  $R^6$  and  $R^7$ , or  $R^7$  and  $R^8$  together with the adjacent carbon atoms in the pyridine ring form a ring wherein the part constituted by  $R^6$  and  $R^7$ , or  $R^7$  and  $R^8$ , is



wherein p is 2, 3 or 4, v is 2 or 3 and the O and N atoms always are attached to position 4 in the pyridine ring; provided that not more than one of  $R^6$ ,  $R^7$  and  $R^8$  is hydrogen can be formulated into an enteric coated dosage form.

The object of the present invention is thus an enteric coated dosage form of acid labile compounds with the general formula I defined above except the compound omeprazole, 5-methoxy-2- (4-methoxy-3,5 dimethyl-2-pyridinyl methyl sulfinyl -1H-benzimidazole. Another compound, which may be enteric coated according to the invention is 2- (2-dimethylaminobenzyl)sulfinyl -benzimidazole. The new preparations are resistant to dissolution in acid media, dissolve rapidly in neutral to alkaline media and have a good stability during long-term storage. The new dosage form is characterized in the following way. Cores containing the acid labile compound mixed with alkaline compounds or an alkaline salt of the acid labile compound optionally mixed with an alkaline compound are coated with two or more layers, whereby the first layer/layers is/are soluble in water or rapidly disintegrating in water and consist(s) of non-acidic, otherwise inert pharmaceutically acceptable substances. This/these first layer/layers separates/separate the alkaline core material from the outer layer, which is an enteric coating. The final, enteric coated dosage form is treated in a suitable way to reduce the water content to a very low level in order to obtain a good

stability of the dosage form during long-term storage.

As examples of compounds especially suitable for the pharmaceutical dosage form according to the invention the compounds listed in Table 1  
5 can be mentioned.

The half-life of degradation of the compounds 1-6 in Table 1 in water solution at pH-values less than four is in most cases shorter than ten minutes. Also at neutral pH-values the degradation reaction proceeds  
10 rapidly, e.g. at pH=7 the half-life of degradation is between 10 minutes and 65 hours while at higher pH-values the stability in solution for most compounds is much better. The stability profile is similar in solid phase. The degradation is catalyzed by acid reacting substances. The acid labile compounds are stabilized in mixtures with alkaline reacting  
15 substances.

From what is said about the stability properties of the acid labile compounds listed above it is obvious that an oral dosage form of the said compounds must be protected from contact with the acid reacting  
20 gastric juice in order to reach the small intestine without degradation.

#### Detailed description of the invention

##### Cores

25

The acid labile active compound is mixed with inert, preferably water soluble, conventional pharmaceutical constituents to obtain the preferred concentration of the active compound in the final mixture and with an alkaline reacting, otherwise inert, pharmaceutically acceptable  
30 substance (or substances), which creates a "micro-pH" around each particle of active compound of not less than pH=7, preferably not less than pH=8, when water is adsorbed to the particles of the mixture or when water is added in small amounts to the mixture. Such substances can be chosen among, but are not restricted to substances such as the  
35 sodium, potassium, calcium, magnesium and aluminium salts of phosphoric acid, carbonic acid, citric acid or other suitable weak inorganic or organic acids; substances normally used in antacid preparations such as

aluminium, calcium and magnesium hydroxides; magnesium oxide or composite substances such as  $\text{Al}_2\text{O}_3 \cdot 6\text{MgO} \cdot \text{CO}_2 \cdot 12\text{H}_2\text{O}$ ,  $(\text{Mg}_6\text{Al}_2(\text{OH})_{16}\text{CO}_3 \cdot 4\text{H}_2\text{O})$ ,  $\text{MgO} \cdot \text{Al}_2\text{O}_3 \cdot 2\text{SiO}_2 \cdot n\text{H}_2\text{O}$ , wherein n not is an integer and less than 2 or similar compounds; organic pH-buffering substances such as trishydroxymethylaminomethane or other similar, pharmaceutically acceptable pH-buffering substances. The stabilizing, high pH-value in the powder mixture can also be achieved by using an alkaline reacting, salt of the active compound such as the sodium, potassium, magnesium, calcium etc. salts of acid labile compounds, either alone or in combination with a conventional buffering substance as previously described.

The powder mixture is then formulated into small beads i.e. pellets or tablets, by conventional pharmaceutical procedures. The pellets, tablets or gelatin capsules are used as cores for further processing.

#### Separating layer

The alkaline reacting cores containing an acid labile compound must be separated from the enteric coating polymer(s) containing free carboxyl groups, which otherwise causes degradation/dicolouration of the acid labile compound during the coating process or during storage. The subcoating layer, (the separating layer), also serves as a pH-buffering zone in which hydrogen ions diffusing from the outside in towards the alkaline core can react with hydroxyl ions diffusing from the alkaline core towards the surface of the coated articles. The pH-buffering properties of the separating layer can be further strengthened by introducing in the layer substances chosen from a group of compounds usually used in antacid formulations such as, for instance, magnesium oxide, hydroxide or carbonate, aluminium or calcium hydroxide, carbonate or silicate; composite aluminium/magnesium compounds such as, for instance  $\text{Al}_2\text{O}_3 \cdot 6\text{MgO} \cdot \text{CO}_2 \cdot 12\text{H}_2\text{O}$ ,  $(\text{Mg}_6\text{Al}_2(\text{OH})_{16}\text{CO}_3 \cdot 4\text{H}_2\text{O})$ ,  $\text{MgO} \cdot \text{Al}_2\text{O}_3 \cdot 2\text{SiO}_2 \cdot n\text{H}_2\text{O}$ , wherein n not is an integer and less than 2 or similar compounds; or other pharmaceutically acceptable pH-buffering substances such as, for instance the sodium, potassium, calcium, magnesium and aluminium salts of phosphoric, citric or other suitable, weak, inorganic or organic acids.

The separating layer consists of one or more water soluble inert layers, optionally containing pH-buffering substances.

5 The separating layer(s) can be applied to the cores - pellets or tablets - by conventional coating procedures in a suitable coating pan or in a fluidized bed apparatus using water and/or conventional organic solvents for the coating solution. The material for the separating layer is chosen among the pharmaceutically acceptable, water soluble, inert compounds or polymers used for film-coating applications such as, for  
10 instance sugar, polyethylene glycol, polyvinylpyrrolidone, polyvinyl alcohol, hydroxypropyl cellulose, hydroxymethyl cellulose, hydroxypropyl methylcellulose or the like. The thickness of the separating layer is not less than 2  $\mu\text{m}$ , for small spherical pellets preferably not less than 4  $\mu\text{m}$ , for tablets preferably not less than 10  $\mu\text{m}$ .

15 In the case of tablets another method to apply the coating can be performed by the drycoating technique. First a tablet containing the acid labile compound is compressed as described above. Around this tablet another layer is compressed using a suitable tableting machine.  
20 The outer, separating layer, consists of pharmaceutically acceptable, in water soluble or in water rapidly disintegrating tablet excipients. The separating layer has a thickness of not less than 1 mm. Ordinary plasticizers, pigments, titanium dioxide talc and other additives may also be included into the separating layer.

25 In the case of gelatin capsules the gelatin capsule itself serves as separating layer.

#### Enteric coating layer

30 The enteric coating layer is applied on to the sub-coated cores by conventional coating techniques such as, for instance, pan coating or fluidized bed coating using solutions of polymers in water and/or suitable organic solvents or by using latex suspensions of said  
35 polymers. As enteric coating polymers can be used, for example, cellulose acetate phthalate, hydroxypropyl methylcellulose phthalate, polyvinyl acetate phthalate, co-polymerized methacrylic acid/methacrylic acid methyl esters such as, for instance, compounds known under the



trade name Eudragit<sup>R</sup> L 12,5 or Eudragit<sup>R</sup> L 100, (Röhm Pharma) or similar compounds used to obtain enteric coatings.

5 The enteric coating can also be applied using water-based polymer dispersions, e.g. Aquateric (FMC Corporation), Eudragit<sup>R</sup> L 100-55 (Röhm Pharma), Coating CE 5142 (BASF). The enteric coating layer can optionally contain a pharmaceutically acceptable plasticizer such as, for instance, cetanol, triacetin, citric acid esters such as, for instance, those known under the trade name Citroflex<sup>R</sup> (Pfizer) phthalic  
10 acid esters, dibutyl succinate or similar plasticizers.

The amount of plasticizer is usually optimized for each enteric coating polymer(s) and is usually in the range of 1-20 % of the enteric coating polymer(s). Dispersants such as talc, colourants and pigments may also  
15 be included into the enteric coating layer.

Thus the special preparation according to the invention consists of cores containing the acid labile compound mixed with an alkaline reacting compound or cores containing an alkaline salt of the acid  
20 labile compound optionally mixed with an alkaline reacting compound. The cores suspended in water forms a solution or a suspension which has a pH, which is higher than that of a solution in which the polymer used for enteric coating is just soluble. The cores are coated with a water soluble or in water rapidly disintegrating coating, optionally  
25 containing a pH-buffering substance, which separates the alkaline cores from the enteric coating. Without this separating layer the resistance towards gastric juice would be too short and the storage stability of the dosage form would be unacceptably short. The sub-coated dosage form is finally coated with an enteric coating rendering the dosage form  
30 insoluble in acid media, but rapidly disintegrating/dissolving in neutral to alkaline media such as, for instance the liquids present in the proximal part of the small intestine, the site where dissolution is wanted.

#### 35 Final dosage form

The final dosage form is either an enteric coated tablet or capsule or in the case of enteric coated pellets, pellets dispensed in hard gelatin

capsules or sachets or pellets formulated into tablets. It is essential for the long term stability during storage that the water content of the final dosage form containing acid labile compound (enteric coated tablets, capsules or pellets) is kept low, preferably not exceeding 1.5 % by weight.

### Process

A process for the manufacture of the oral dosage form represents a further aspect of the invention. After the forming of the cores the cores are first coated with the separating layer and then with the enteric coating layer. The coating is carried out as described above.

The preparation according to the invention is especially advantageous in reducing gastric acid secretion and/or providing a gastrointestinal cytoprotective effect. It is usually administered one to several times a day. The typical daily dose of the active substance varies and will depend on various factors such as for example the individual requirement of the patients, the mode of administration and the disease. In general the dosage will be in the range of 1 to 400 mg per day of active substance. A method for the treatment of such conditions using the novel oral dosage form represents a further aspect of the invention.

The invention is described in detail in the following examples:

### EXAMPLES

Examples 1 - 3 exemplify the invention.

#### Example 1

##### Uncoated pellets

35	I	{	Lactose powder	253	g
			Lactose anhydrous	167	g
			Hydroxypropyl cellulose	25	g

II	Compound 1, Table I	50 g
	Sodium lauryl sulphate	5 g
	Disodium hydrogen phosphate	1.5 g
	Sodium dihydrogen phosphate	0.1 g
	Distilled water	125 g

5

The dry ingredients (I) were premixed in a mixer. Addition of a granulation liquid (II) containing the suspended active compound was made and the mass was wet-mixed to a proper consistency. The wet mass  
 10 was pressed through an extruder and spheronized to pellets. The pellets were dried and classified into suitable particle size ranges.

#### Subcoated pellets

III	Uncoated pellets	500 g
	Hydroxypropyl methyl-	
	cellulose	20 g
	Distilled water	400 g

20 The polymer solution (III) was sprayed onto the uncoated pellets in a fluidized bed apparatus. The spray guns were placed above the fluidized bed.

#### Enteric coated pellets

25

IV	Subcoated pellets	500 g
	Hydroxypropyl methylcellulose	
	phthalate	57 g
	Cetyl alcohol	3 g
	Acetone	540 g
	Ethanol	231 g

30

The polymer solution (IV) was sprayed on the subcoated pellets in a fluidized bed apparatus with spray guns placed above the bed. After  
 35 drying to a water content of 0.5 % the enteric coated pellets were classified and filled into hard gelatin capsules in an amount of 284 mg, corresponding to 25 mg of active compound 1. 30 capsules were packed in tight containers together with a desiccant.

Example 2

Formulation with the sodium salt of compound 2 according to Table I.

5 Uncoated pellets

10	I	{	Compound 2, Table I sodium salt	339	g
			Mannitol powder	2 422	g
			Lactose anhydrous	120	g
			Hydroxypropyl cellulose	90	g
			Microcrystalline cellulose	60	g
15	II	{	Sodium lauryl sulphate	7	g
			Distilled water	650	g

The preparation was made as described in Example 1 with the exception that the sodium salt of compound 2 was added together with the other ingredients in mixture I.

20 Subcoated pellets

25	III	{	Uncoated pellets	500	g
			Hydroxypropyl methylcellulose	20	g
			Aluminium hydroxide/magnesium carbonate	4	g
			Distilled water	400	g
30	IV	{	Pellets subcoated with III	500	g
			Hydroxypropyl methylcellulose	20	g
			Distilled water	400	g

The two subcoat layers, III and IV, were applied to the uncoated pellets in a fluidized bed apparatus in consecutive order as previously described.

Enteric coated pellets

	Subcoated pellets	500	g
5	{ Hydroxypropyl methylcellulose		
	{ phthalate	57	g
	{ Cetyl alcohol	3	g
	{ Acetone	540	g
	{ Ethanol	231	g

- 10 The preparation of enteric coated pellets was performed as described in Example 1.

Example 3

- 15 Formulation with compound 6, according to Table 1. This example gives the composition of one unit dose according to the invention.

Tablet core

20	Compound 6, Table 1	15 mg
	Lactose	119 mg
	Hydroxypropyl cellulose (low substitution)	5 mg
	Hydroxypropyl cellulose	1 mg
25	Talc	5 mg
	Mg(OH) <sub>2</sub>	<u>15 mg</u>
	Total	160 mg

- 30 Tablet cores having the composition above and each weighing 160 mg were first made by known techniques.

Separating layer (inner)

	Hydroxypropyl cellulose	2 mg
35	Synthetic hydrotalcite	0.3 mg
	[Al <sub>2</sub> O <sub>3</sub> .6MgO.CO <sub>2</sub> .12H <sub>2</sub> O]	

Separating layer (outer)

Hydroxypropyl cellulose 2 mg

- 5 The two separating layers were applied to the cores by known coating techniques.

Enteric coating layer

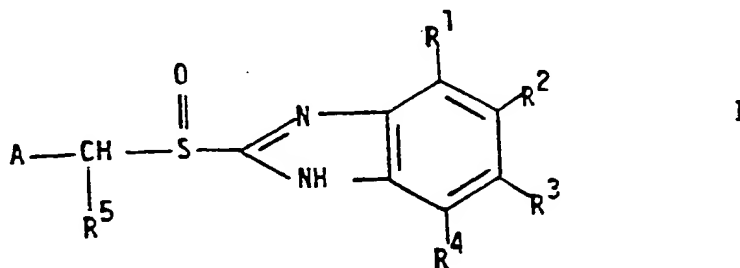
- 10 Hydroxypropyl methylcellulose  
phthalate 7 mg  
Cetyl alcohol 0.5 mg

- The enteric coating solution was sprayed on the cores coated by the two  
15 separating layers by known enteric coating techniques.

CLAIMS

1. An oral, pharmaceutical preparation containing an acid labile compound as the active ingredient characterized in that it is composed of core material containing the active ingredient together with an alkaline reacting compound, or an alkaline salt of the active ingredient optionally together with an alkaline reacting compound, and on said core material one or more inert reacting subcoating layers comprising tablet excipients which are soluble or rapidly disintegrating in water, or polymeric, water soluble, filmforming compounds, optionally containing pH-buffering, alkaline compounds between the alkaline reacting core and an outer layer, which is an enteric coating.

2. A preparation according to claim 1, wherein the acid labile compound has the general formula I.



wherein A is an optionally substituted heterocyclic group, R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> are the same or different and preferably hydrogen,

lower alkyl, lower alkoxy, -CF<sub>3</sub>, -O-C(=O)-lower alkyl or halogen and R<sup>5</sup> is H or a lower alkyl group wherein "lower" denotes 1-6 carbon atoms except the compound omeprazole, 5-methoxy-2-[[[(4-methoxy-3,5 dimethyl-2-pyridinyl) methyl] sulfinyl] -1H-benzimidazole; or the acid labile compound is 2-[(2-dimethylaminobenzyl)sulfinyl]-benzimidazole.

3. A preparation according to claim 1 wherein the subcoating layer comprises one or more of magnesium oxide, magnesium hydroxide or composite substance [Al<sub>2</sub>O<sub>3</sub>·6MgO·CO<sub>2</sub>·12H<sub>2</sub>O or MgO·Al<sub>2</sub>O<sub>3</sub>·2SiO<sub>2</sub>·nH<sub>2</sub>O], wherein n not is an integer and less than two.

4. A preparation according to claim 2 or 3 wherein the subcoating comprises two or more sub-layers.
5. A preparation according to claim 4 wherein the subcoating comprises  
5 hydroxypropyl methylcellulose, hydroxypropyl cellulose or polyvinyl-  
pyrrolidone.
6. A preparation according to claim 1 wherein the alkaline core  
comprises the acid labile compound and pH-buffering alkaline compound  
10 rendering to the micro-environment of the acid labile compound a pH of  
7-12.
7. A preparation according to claim 6 wherein the alkaline compound  
comprises one or more of magnesium oxide, hydroxide or carbonate,  
15 aluminium hydroxide, aluminium, calcium, sodium or potassium carbonate,  
phosphate or citrate, the composite aluminium/magnesium compounds  
 $\text{Al}_2\text{O}_3 \cdot 6\text{MgO} \cdot \text{CO}_2 \cdot 12\text{H}_2\text{O}$  or  $\text{MgO} \cdot \text{Al}_2\text{O}_3 \cdot 2\text{SiO}_2 \cdot n\text{H}_2\text{O}$ , wherein n not is an  
integer and less than two.
- 20 8. A preparation according to claim 1 wherein the alkaline core  
comprises an alkaline salt of the acid labile compound such as the  
sodium, potassium, magnesium, calcium or ammonium salt.
9. A preparation according to claim 7 wherein the alkaline core  
25 comprises an alkaline salt of the acid labile compound mixed with an  
inert, alkaline compound.
10. A preparation according to claim 1 wherein the enteric coating  
comprises hydroxypropyl methylcellulose phthalate, cellulose acetate  
30 phthalate, co-polymerized methacrylic acid/methacrylic acid methyl ester  
or polyvinyl acetate phthalate, optionally containing a plasticizer.
11. A preparation according to claim 1 wherein the water content of the  
final dosage form containing the acid labile compound does not  
35 exceed 1.5 % by weight.



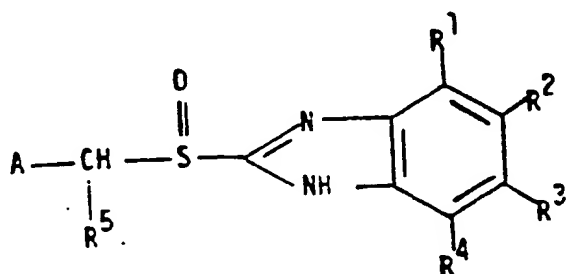
12. Process for the preparation of an oral pharmaceutical formulation containing an acid labile compound in which cores containing the acid labile compound mixed with an alkaline reacting compound or compounds or an alkaline salt of the acid labile compound optionally mixed with an  
5 alkaline reacting compound or compounds are coated with one or more inert reacting subcoating layers whereafter the subcoated cores are further coated with an enteric coating layer.

13. Use of the preparation according to claim 1 for the manufacture of a  
10 medicament for treatment of gastrointestinal diseases.

CLAIMS FOR THE CONTRACTING STATES AT, ES, GR.

1. A process for the preparation of an oral, pharmaceutical formulation containing an acid labile compound as the active ingredient characterized in that the cores containing the acid labile compound mixed with an alkaline reacting compound, or an alkaline salt of the active ingredient optionally together with an alkaline reacting compound, are coated with one or more inert reacting subcoating layers comprising tablet excipients which are soluble or rapidly disintegrating in water, or polymeric, water soluble, filmforming compounds, optionally containing pH-buffering, alkaline compounds between the alkaline reacting core and an outer layer, which is an enteric coating layer, whereafter the subcoated cores are further coated with said outer enteric coating layer.

2. A process according to claim 1, wherein the acid labile compound has the general formula I.



wherein A is an optionally substituted heterocyclic group, R¹, R², R³ and R⁴ are the same or different and preferably hydrogen,

lower alkyl, lower alkoxy, -CF₃, -O-C(=O)-lower alkyl or halogen and R⁵ is H or a lower alkyl group wherein "lower" denotes 1-6 carbon atoms except the compound omeprazole, 5-methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridinyl] methyl] sulfinyl] -1H-benzimidazole; or the acid labile compound is 2-[(2-dimethylaminobenzyl)sulfinyl]-benzimidazole.

3. A process according to claim 1 wherein the subcoating layer comprises one or more of magnesium oxide, magnesium hydroxide or composite

substance  $[Al_2O_3 \cdot 6MgO \cdot CO_2 \cdot 12H_2O \text{ or } MgO \cdot Al_2O_3 \cdot 2SiO_2 \cdot nH_2O]$ , wherein n not is an integer and less than two.

4. A process according to claim 2 or 3 wherein the subcoating comprises two or more sub-layers.
5. A process according to claim 4 wherein the subcoating comprises hydroxypropyl methylcellulose, hydroxypropyl cellulose or polyvinyl-pyrrolidone.
6. A process according to claim 1 wherein the alkaline core comprises the acid labile compound and pH-buffering alkaline compound rendering to the micro-environment of the acid labile compound a pH of 7-12.
7. A process according to claim 6 wherein the alkaline compound comprises one or more of magnesium oxide, hydroxide or carbonate, aluminium hydroxide, aluminium, calcium, sodium or potassium carbonate, phosphate or citrate, the composite aluminium/magnesium compounds  $Al_2O_3 \cdot 6MgO \cdot CO_2 \cdot 12H_2O$  or  $MgO \cdot Al_2O_3 \cdot 2SiO_2 \cdot nH_2O$ , wherein n not is an integer and less than two.
8. A process according to claim 1 wherein the alkaline core comprises an alkaline salt of the acid labile compound such as the sodium, potassium, magnesium, calcium or ammonium salt.
9. A process according to claim 7 wherein the alkaline core comprises an alkaline salt of the acid labile compound mixed with an inert, alkaline compound.
10. A process according to claim 1 wherein the enteric coating comprises hydroxypropyl methylcellulose phthalate, cellulose acetate phthalate, co-polymerized methacrylic acid/methacrylic acid methyl ester or polyvinyl acetate phthalate, optionally containing a plasticizer.
11. A process according to claim 1 wherein the water content of the final dosage form containing the acid labile compound does not exceed 1.5 % by weight.

12. Use of the formulation prepared according to claim 1 for the manufacture of a medicament for treatment of gastrointestinal diseases.



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EP-A- 247 983 EP-A- 0 080 602  
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DE-A- 3 233 764 FR-A- 2 272 639  
GB-A- 760 403 GB-A- 1 190 387

PATENT ABSTRACTS OF JAPAN, vol. 8, no.  
106 (C-223)[1543], 18 May 1984.

SCANDINAVIAN JOURNAL OF GASTROEN-  
TEROLOGY, vol. 20, supplement 108(1985).

BROCHURE ON HPCM TC-5, Shinetsa Chemi-  
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EP 0 244 380 B1

UP TO DATE PHARMACEUTICAL TECHNOLOGY, series no. 1: Coating of Drugs, 1969.

ACTA CHEMICA SCANDINAVICA, vol. 43, 1989 (reprint), no. 6; pp. 536-611.

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## Description

The present invention is related to new pharmaceutical preparations containing acid labile substances for oral use and, to a method for the manufacture of such preparations.

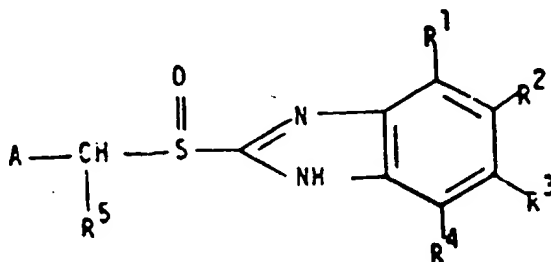
5 Acid labile substances present a problem to the formulator when formulating a pharmaceutical dosage form for oral use. In order to prevent the substances from contact with the acid reacting gastric juice after oral intake, the conventional way to solve this problem is to coat the dosage form with an enteric coating. The coating is a group of substances/polymers with the common feature of being practically insoluble in acid media, while they are soluble in neutral to alkaline media. For substances that are labile in acid media,  
 10 but have better stability in neutral to alkaline media, it is often advantageous to add alkaline reacting inactive constituents in order to increase the stability of the active compound during manufacture and storage.

A group of compounds exerting these stability properties are substituted benzimidazoles with the general formula I

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20

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wherein A is an optionally substituted heterocyclic group and R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, and R<sup>4</sup>, are the same or different as defined below and R<sup>5</sup> is H or a lower alkyl, or the compound 2-[(2-dimethylaminobenzyl)sulfinyl]-  
 30 benzimidazole.

The compounds with the general formula I are virtually biologically inactive as such, but degrade/transform to active inhibitors of certain enzyme systems in acid media.

As examples of compounds with the mentioned properties the compounds described in the patents US-A-4045 563, EP-B1-0 005 129 and BE-898 880 and the patent applications, EP-A-173664, EP-A1-0 080 602,  
 35 EP-0127 763, EP-0 134 400, EP-0 130 729, EP-0 150 586, DE-3415971 GB-2 082 580 and SE-A-8504048-3 may be mentioned. The last application describes 2- (2-disubstituted-aminobenzyl)sulfinyl benzimidazoles, e.g. 2- (2-di-methylaminobenzyl)sulfinyl benzimidazole, also called, NC-1300 and presented by Prof. S. Okabe at the Symposium on Drug Activity held on Oct 17th 1985 in Nagoya, Japan, and which interacts with the H<sup>+</sup>K<sup>+</sup>-ATPase after acid degradation within the parietal cells. (See for instance B. Wallmark, A.  
 40 Brändström and H. Larsson "Evidence for acid-induced transformation of omeprazole into an active inhibitor of H<sup>+</sup>K<sup>+</sup>-ATPase within the parietal cell", Biochemica et Biophysica Acta 778, 549-558, 1984). Other compounds with similar properties are further mentioned in the patent US-4 182 766 and the patent applications GB-2 141 429, EP-0 146 370 and GB-2 082 580. A common feature of these compounds is that they are transformed into the biologically active compounds via rapid degradation/transformation in acid  
 45 media.

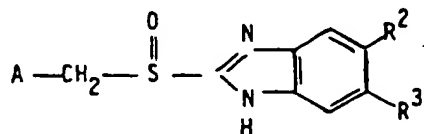
The stability profile of some compounds with the general formula I above is exemplified in the Table 1 below, where the half-life of the degradation/transformation reaction in solution at pH 2 and 7 are given.

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Table 1. Rate of degradation/transformation of compounds  
with the general structure

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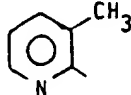


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Compound No	A	R <sup>2</sup>	R <sup>3</sup>	Half-life (minutes) for the transformation to the active moiety	
				at pH = 2	at pH = 7

15

20

1.		5-COOCH <sub>3</sub> ;	6-CH <sub>3</sub>	11	150
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25

2.		5-CH <sub>3</sub> ;	H	5.4	1700
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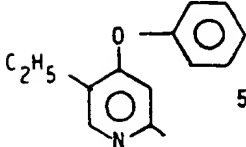
3.		5-CF <sub>3</sub> ;	H	1.9	122
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4.		5-CF <sub>3</sub> ;	H	2.0	8.8
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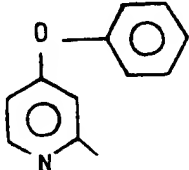
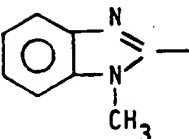
5.		5-OCH <sub>3</sub> ;	H	3.7	1620
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Cont.

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Compound No	A	R <sup>2</sup>	R <sup>3</sup>	Half-life (minutes) for the transformation to the active moiety	
				at pH = 2	at pH = 7
6.		5-OCH <sub>3</sub> ;	H	4.0	3900
7.		5-C <sub>2</sub> H <sub>5</sub> ;	H	33	not determined

Substituted sulfoxides, such as for instance the substituted benzimidazoles described in EP-B1-0005129 are potent inhibitors of gastric acid secretion. The substituted benzimidazoles are susceptible to degradation/transformation in acid reacting and neutral media.

It is an inherent property of these compounds to be activated to the active moiety in the acid environment within the parietal cells. The activated compound interacts with the enzyme in the parietal cells, which mediates the production of hydrochloric acid in the gastric mucosa. All compounds of the class of substituted benzimidazoles, containing a sulfoxide grouping, which interferes with the H<sup>+</sup>K<sup>+</sup>-ATPase in the parietal cells hitherto known are all also degraded in acid media.

A pharmaceutical dosage form of acid labile substances, which prevents the substances from contact with acidic gastric juice, must be enteric coated. Ordinary enteric coatings, however, are made of acidic compounds. If covered with such a conventional enteric coating, the acid labile substance rapidly decomposes by direct or indirect contact with it, with the result that the preparations become badly discoloured and lose in content of the active compound with the passage of time.

In order to enhance the storage stability, the cores which contain the acid labile substance must also contain alkaline reacting constituents. When such an alkaline core is enteric coated with an amount of a conventional enteric coating polymer such as, for example, cellulose acetate phthalate, that permits the dissolution of the coating and the active drug contained in the cores in the proximal part of the small intestine, it also will allow some diffusion of water or gastric juice through the enteric coating into the cores, during the time the dosage form resides in the stomach before it is emptied into the small intestine. The diffused water or gastric juice will dissolve parts of the core in the close proximity of the enteric coating layer and there form an alkaline solution inside the coated dosage form. The alkaline solution will interfere with the enteric coating and eventually dissolve it.

In DE-A1-3 046 559 a way to coat a dosage form is described. First the dosage form is coated with a water insoluble layer containing microcrystalline cellulose and then with a second enteric coating with the aim to achieve a dosage form which releases the active drug in the colon. This method of preparation will not give the desired release of the compounds with the general formula I above in the small intestine.

US-A-2 540 979 describes an enteric coated oral dosage form, where the enteric coating is combined with a second and/or first coating of a water insoluble "wax" layer. This method of preparation is not applicable on cores containing a compound with the general formula I since direct contact between substances such as cellulose acetate phthalate (CAP) and a compound of formula I causes degradation and discolouration of the compounds of the formula I.

DE-B2-23 36 218 describes a method to produce a dialysis membrane consisting of a mixture of one or more conventional enteric coating polymers and one or more insoluble cellulose derivatives. Such a

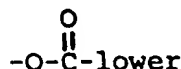
membrane will not give a proper protection of the acid labile compounds of the formula I in gastric juice.

DE-A1-1 204 363 describes a three-layer coating procedure. The first layer is soluble in gastric but is insoluble in intestinal juice. The second is water soluble regardless of pH and the third layer is an enteric coating. This preparation as well as the preparation described in DE-A1-1 617 615 result in a dosage form which is not dissolved in gastric juice and which only dissolves slowly in intestinal juice. Such preparations cannot be used for the compounds of the formula I, where a rapid release of the drug in the small intestine is needed. DE-A1 12 04 363 describes coating with three layers to achieve release of a drug in the ileum, an aim which is outside the scope of the present invention. GB-A-1 485 676 describes a way to obtain a preparation which effervesces in the small intestine. This is obtained by the enteric coating of a core containing the active drug and an effervescing system such as a combination of carbonate and/or bicarbonate salt and a pharmaceutically acceptable acid. This formulation cannot be adopted for a pharmaceutical dosage form containing a compound of formula I as the presence of an acid in contact with a compound of formula I in the cores would give as a result that the compound of formula I was degraded.

WO 85/03436 describes a pharmaceutical preparation, wherein cores containing active drugs mixed with for instance buffering components such as sodium dihydrogen-phosphate with the aim of maintaining a constant pH and a constant rate of diffusion, are coated with a first coating which controls the diffusion. This formulation cannot be adopted for acid labile compounds where a rapid release in the small intestine is wanted. Direct application of an enteric coating onto the cores would also adversely influence the storage stability of such dosage forms containing acid labile compounds.

EP-A-124 495 and EP-A-173 664 describe enteric coated granules without subcoating or a powder that are filled into hard gelatine capsules or a solution that is filled into a soft capsule.

The object of the present invention is to provide an oral, pharmaceutical preparation stable to discolouration containing an acid labile compound of the general formula I above wherein A is an optionally substituted heterocyclic group, R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup>, are the same or different and preferably hydrogen, lower alkyl, lower alkoxy, -CF<sub>3</sub>.



alkyl or halogen and R<sup>5</sup> is H or a lower alkyl group wherein "lower" denotes 1-6 carbon atoms except the compound omeprazole, methoxy-2-[(4-methoxy-3,5 dimethyl-2-pyridinyl) methyl] sulfinyl]-1H-benzimidazole; or the acid labile compound is 2-[(2-dimethylaminobenzyl)sulfinyl]-benzimidazole as the active ingredient. The core material is in the form of small beads or tablets containing the active ingredient together with an alkaline reacting compound, or an alkaline salt of the active ingredient optionally together with an alkaline reacting compound, and on said core material one or more inert reacting subcoating layers comprising tablet excipients which are soluble or rapidly disintegrating in water, or polymeric, water soluble, filmforming compounds, optionally containing pH-buffering, alkaline compounds between the alkaline reacting core and an outer layer, which is an enteric coating.

R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup>, which are the same or different and especially

- (a) hydrogen
- (b) halogen, e.g. F, Cl, Br, I
- (c) -CN
- (d) -CHO
- (e) -CF<sub>3</sub>
- (f)



- (g) -O-C-R<sup>12</sup>
- (h) -CH(OR<sup>13</sup>)<sub>2</sub>
- (i) -(Z)<sub>n</sub>-B-D
- (j) aryl containing up to 10 carbon atoms
- (k) aryloxy containing up to 10 carbon atoms, optionally substituted by alkyl containing 1-6 carbon atoms
- (l) -alkylthio containing 1-6 carbon atoms

(m) -NO<sub>2</sub>

(n) -alkylsulfinyl containing 1-6 carbon atoms

(o) or wherein adjacent groups R<sup>1</sup> R<sup>2</sup> R<sup>3</sup> and R<sup>4</sup> together with the adjacent carbon atoms in the benzimidazole ring form a 5-, 6- or 7-membered monocyclic ring or a 9-, 10- or 11-membered bicyclic ring, which rings may be saturated or unsaturated and may contain 0-3 hetero atoms selected from -N- and -O-, and which rings may be optionally substituted with 1-4 substituents selected from alkyl groups with 1-3 carbon atoms, alkylene radicals containing 4-5 carbon atoms giving spiro compounds, or two or four of these substituents together form one or two oxo groups



whereby if R<sup>1</sup> and R<sup>2</sup>, R<sup>2</sup> and R<sup>3</sup> or R<sup>3</sup> and R<sup>4</sup> together with the adjacent carbon atoms in the benzimidazole ring form two rings they may be condensed with each other, in which formulas R<sup>11</sup> and R<sup>12</sup>, which are the same or different, are

(a) aryl containing up to 10 carbon atoms

(b) alkoxy containing 1-4 carbon atoms

(c) alkoxyalkoxy containing 1-3 carbon atoms in each alkoxy part

(d) arylalkoxy containing 1-2 carbon atoms in the alkoxy part and up to 10 carbon atoms in the aryl part

(e) aryloxy containing up to 10 carbon atoms

(f) dialkylamino containing 1-3 carbon atoms in the alkyl parts, or

(g) pyrrolidino or piperidino, optionally substituted with alkyl containing 1-3 carbon atoms;

R<sup>13</sup> is

(a) alkyl containing 1-4 carbon atoms, or

(b) alkylene containing 2-3 carbon atoms;

Z is -O- or



n is 0 or 1;

B is

(a) alkylene containing 1-6 carbon atoms

(b) cycloalkylene containing 3-6 carbon atoms

(c) alkenylene containing 2-6 carbon atoms

(d) cycloalkylene containing 3-6 carbon atoms, or

(e) alkenylene containing 2-6 carbon atoms;

D is

(a) H

(b) -CN

(c)



(d) -(Y)<sub>m</sub>



wherein  
R<sup>9</sup> is

- (a) alkoxy containing 1-5 carbon atoms, or  
(b) dialkylamino containing 1-3 carbon atoms in the alkyl parts;

m is 0 or 1;  
r is 0 or 1;  
Y is

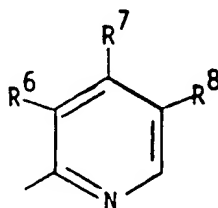
- (a) -O-  
(b) -NH-  
(c) -NR<sup>10</sup>-;

R<sup>10</sup> is

- (a) H  
(b) alkyl containing 1-3 carbon atoms  
(c) arylalkyl containing 1-2 carbon atoms in the alkyl part and up to 10 carbon atoms in the aryl part  
(d) aryl containing up to 10 carbon atoms;

R<sup>5</sup> is H, CH<sub>3</sub> or C<sub>2</sub>H<sub>5</sub>;

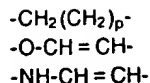
A is especially a pyridyl group in which R<sup>6</sup> and R<sup>8</sup> are the same or different, are



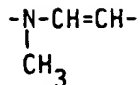
(a) H or  
(b) alkyl containing 1-6 carbon atoms;  
R<sup>7</sup> is

- (a) H  
(b) alkyl containing 1-8 carbon atoms  
(c) alkoxy containing 1-8 carbon atoms  
(d) alkenyloxy containing 2-5 carbon atoms  
(e) alkynyloxy containing 2-5 carbon atoms  
(f) alkoxyalkoxy containing 1-2 carbon atoms in each alkoxy group  
(g) aryl containing up to 10 carbon atoms  
(h) arylalkyl containing 1-6 carbon atoms in the alkyl part and up to 10 carbon atoms in the aryl part  
(i) aryloxy containing up to 10 carbon atoms, optionally substituted by alkyl containing 1-6 carbon atoms  
(j) arylalkoxy containing 1-6 carbon atoms in the alkoxy part and up to 10 carbon atoms in the aryl part  
(k) dialkylaminoalkoxy containing 1-2 carbon atoms in the alkyl substituents on the amino nitrogen and 1-4 carbon atoms in the alkoxy group  
(l) oxacycloalkyl containing one oxygen atom and 3-7 carbon atoms  
(m) oxacycloalkoxy containing two oxygen atoms and 4-7 carbon atoms  
(n) oxacycloalkylalkyl containing one oxygen atom and 4-7 carbon atoms  
(o) oxacycloalkylalkoxy containing two oxygen atoms and 4-6 carbon atoms, or  
(p) R<sup>6</sup> and R<sup>7</sup>, or R<sup>7</sup> and R<sup>8</sup> together with the adjacent carbon atoms in the pyridine ring form a ring wherein the part constituted by R<sup>6</sup> and R<sup>7</sup>, or R<sup>7</sup> and R<sup>8</sup>, is

-CH=CH-CH=CH-  
-O-(CH<sub>2</sub>)<sub>p</sub>-  
-S-(CH<sub>2</sub>)<sub>v</sub>-



5



10 wherein p is 2, 3 or 4, v is 2 or 3 and the O and N atoms always are attached to position 4 in the pyridine ring; provided that not more than one of R<sup>6</sup>, R<sup>7</sup> and R<sup>8</sup> is hydrogen can be formulated into an enteric coated dosage form.

The object of the present invention is thus an enteric coated dosage form of acid labile compounds with the general formula I defined above except the compound omeprazole, 5-methoxy-2-[[[4-methoxy-3,5  
15 dimethyl-2-pyridinyl)methyl]sulfinyl] -1H-benzimidazole. Another compound, which may be enteric coated according to the invention is 2- (2-dimethylaminobenzyl)sulfinyl -benzimidazole. The new preparations are resistant to dissolution in acid media, dissolve rapidly in neutral to alkaline media and have a good stability during long-term storage. The new dosage form is characterized in the following way. Cores containing the acid labile compound mixed with alkaline compounds or an alkaline salt of the acid labile compound  
20 optionally mixed with an alkaline compound are coated with two or more layers, in which the first layer/layers is/are soluble in water or rapidly disintegrating in water and consist(s) of non-acidic, otherwise inert pharmaceutically acceptable substances. This/these first layer/layers separates/separate the alkaline core material from the outer layer, which is an enteric coating. The final, enteric coated dosage form is treated in a suitable way to reduce the water content to a very low level in order to obtain a good stability  
25 with virtually no discolouration of the dosage form during long-term storage.

As examples of compounds especially suitable for the pharmaceutical dosage form according to the invention the compounds listed in Table 1 can be mentioned.

The half-life of degradation of the compounds 1-6 in Table 1 in water solution at pH-values less than four is in most cases shorter than ten minutes. Also at neutral pH-values the degradation reaction proceeds  
30 rapidly, e.g. at pH=7 the half-life of degradation is between 10 minutes and 65 hours while at higher pH-values the stability in solution for most compounds is much better. The stability profile is similar in solid phase. The degradation is catalyzed by acid reacting substances. The acid labile compounds are stabilized in mixtures with alkaline reacting substances.

From what is said about the stability properties of the acid labile compounds listed above it is obvious  
35 that an oral dosage form of the said compounds must be protected from contact with the acid reacting gastric juice in order to reach the small intestine without degradation.

#### Cores

40 The acid labile active compound is mixed with inert, preferably water soluble, conventional pharmaceutical constituents to obtain the preferred concentration of the active compound in the final mixture and with an alkaline reacting, otherwise inert, pharmaceutically acceptable substance (or substances), which creates a "micro-pH" around each particle of active compound of not less than pH=7, preferably not less than pH=8, when water is adsorbed to the particles of the mixture or when water is added in small amounts to the  
45 mixture. Such substances can be chosen among substances such as the sodium, potassium, calcium, magnesium and aluminium salts of phosphoric acid, carbonic acid, citric acid or other suitable weak inorganic or organic acids; substances normally used in antacid preparations such as aluminium, calcium and magnesium hydroxides; magnesium oxide or composite substances such as  $\text{Al}_2\text{O}_3 \cdot 6\text{MgO} \cdot \text{CO}_2 \cdot 12\text{H}_2\text{O}$ ,  $(\text{Mg}_6\text{Al}_2(\text{OH})_{16}\text{CO}_3 \cdot 4\text{H}_2\text{O})$ ,  $\text{MgO} \cdot \text{Al}_2\text{O}_3 \cdot 2\text{SiO}_2 \cdot n\text{H}_2\text{O}$ , wherein n not is an integer and less than 2 or similar  
50 compounds; organic pH-buffering substances such as trishydroxymethylaminomethane or other similar, pharmaceutically acceptable pH-buffering substances. The stabilizing, high pH-value in the powder mixture can also be achieved by using an alkaline reacting, salt of the active compound such as the sodium, potassium, magnesium, calcium salts of acid labile compounds, either alone or in combination with a conventional buffering substance as previously described.

55 The powder mixture is then formulated into small beads i.e. pellets or tablets, by conventional pharmaceutical procedures. The pellets or tablets are used as cores for further processing.

#### Separating layer

The alkaline reacting cores containing an acid labile compound must be separated from the enteric coating polymer(s) containing free carboxyl groups, which otherwise causes degradation/discolouration of the acid labile compound during the coating process or during storage. The subcoating layer, (the separating layer), also serves as a pH-buffering zone in which hydrogen ions diffusing from the outside in towards the alkaline core can react with hydroxyl ions diffusing from the alkaline core towards the surface of the coated particles. The pH-buffering properties of the separating layer can be further strengthened by introducing in the layer substances chosen from a group of compounds usually used in antacid formulations such as, for instance, magnesium oxide, hydroxide or carbonate, aluminium or calcium hydroxide, carbonate or silicate; composite aluminium/magnesium compounds such as, for instance  $\text{Al}_2\text{O}_3 \cdot 6\text{MgO} \cdot 12\text{H}_2\text{O}$ ,  $(\text{Mg}_6\text{Al}_2(\text{OH})_{16}\text{CO}_3 \cdot 4\text{H}_2\text{O})$ ,  $\text{MgO} \cdot \text{Al}_2\text{O}_3 \cdot 2\text{SiO}_2 \cdot n\text{H}_2\text{O}$ , wherein n not is an integer and less than 2 or similar compounds; or other pharmaceutically acceptable pH-buffering substances such as, for instance the sodium, potassium, calcium, magnesium and aluminium salts of phosphoric, citric or other suitable, weak, inorganic or organic acids.

The separating layer consists of one or more water soluble inert layers, optionally containing pH-buffering substances.

The separating layer(s) can be applied to the cores - pellets or tablets - by conventional coating procedures in a suitable coating pan or in a fluidized bed apparatus using water and/or conventional organic solvents for the coating solution. The material for the separating layer is chosen among the pharmaceutically acceptable, water soluble, inert compounds or polymers used for film-coating applications such as, for instance sugar, polyethylene glycol, polyvinylpyrrolidone, polyvinyl alcohol, hydroxypropyl cellulose, hydroxymethyl cellulose or hydroxypropyl methylcellulose. The thickness of the separating layer is not less than 2  $\mu\text{m}$ , for small spherical pellets preferably not less than 4  $\mu\text{m}$ , for tablets preferably not less than 10  $\mu\text{m}$ .

In the case of tablets another method to apply the coating can be performed by the drycoating technique. First a tablet containing the acid labile compound is compressed as described above. Around this tablet another layer is compressed using a suitable tableting machine. The outer, separating layer, consists of pharmaceutically acceptable, in water soluble or in water rapidly disintegrating tablet excipients. The separating layer has a thickness of not less than 1 mm. Ordinary plasticizers, pigments, titanium dioxide talc and other additives may also be included into the separating layer.

The enteric coating layer is applied on to the sub-coated cores by conventional coating techniques such as, for instance, pan coating or fluidized bed coating using solutions of polymers in water and/or suitable organic solvents or by using latex suspensions of said polymers. As enteric coating polymers can be used, for example, cellulose acetate phthalate, hydroxypropyl methylcellulose phthalate, polyvinyl acetate phthalate, co-polymerized methacrylic acid/methacrylic acid methyl esters such as, for instance, compounds known under the trade name Eudragit<sup>®</sup> L 12,5 or Eudragit<sup>®</sup> L 100, (Röhm Pharma) or similar compounds used to obtain enteric coatings.

The enteric coating can also be applied using water-based polymer dispersions, e.g. Aquateric (FMC Corporation), Eudragit<sup>®</sup> L 100-55 (Röhm Pharma), Coating CE 5142 (BASF). The enteric coating layer can optionally contain a pharmaceutically acceptable plasticizer such as, for instance, cetanol, triacetin, citric acid esters such as, for instance, those known under the trade name Citrofex<sup>®</sup> (Pfizer) phthalic acid esters, dibutyl succinate or similar plasticizers.

The amount of plasticizer is usually optimized for each enteric coating polymer(s) and is usually in the range of 1-20 % of the enteric coating polymer(s). Dispersants such as talc, colourants and pigments may also be included into the enteric coating layer.

Thus the special preparation according to the invention consists of cores containing the acid labile compound mixed with an alkaline reacting compound or cores containing an alkaline salt of the acid labile compound optionally mixed with an alkaline reacting compound. The cores suspended in water forms a solution or a suspension which has a pH, which is higher than that of a solution in which the polymer used for enteric coating is just soluble. The cores are coated with a water soluble or in water rapidly disintegrating coating, optionally containing a pH-buffering substance, which separates the alkaline cores from the enteric coating. Without this separating layer the resistance towards gastric juice would be too short and the storage stability of the dosage form would be unacceptably short. The sub-coated dosage form is finally coated with an enteric coating rendering the dosage form insoluble in acid media, but rapidly disintegrating/dissolving in neutral to alkaline media such as, for instance the liquids present in the proximal part of the small intestine, the site where dissolution is wanted.

#### Final dosage form

The final dosage form is either an enteric coated tablet or in the case of enteric coated pellets, pellets

dispensed in hard gelatin capsules or sachets or pellets formulated into tablets. It is essential for the long term stability during storage that the water content of the final dosage form containing acid labile compound (enteric coated tablets, capsules or pellets) is kept low, preferably not exceeding 1.5 % by weight.

A process for the manufacture of the oral dosage form represents a further aspect of the invention. After the forming of the cores the cores are first coated with the separating layer and then with the enteric coating layer. The coating is carried out as described above.

The preparation according to the invention is especially advantageous in reducing gastric acid secretion and/or providing a gastrointestinal cytoprotective effect. It is usually administered one to several times a day. The typical daily dose of the active substance varies and will depend on various factors such as for example the individual requirement of the patients, the mode of administration and the disease. In general the dosage will be in the range of 1 to 400 mg per day of active substance.

The invention is described in detail in the following examples:

#### EXAMPLES

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Examples 1 - 3 exemplify the invention.

#### Example 1

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##### Uncoated pellets

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I	{	Lactose powder	253	g
		Lactose anhydrous	167	g
		Hydroxypropyl cellulose	25	g

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II	{	Compound 1, Table I	50	g
		Sodium lauryl sulphate	5	g
		Disodium hydrogen phosphate	1.5	g
		Sodium dihydrogen phosphate	0.1	g
		Distilled water	125	g

40

The dry ingredients (I) were premixed in a mixer. Addition of a granulation liquid (II) containing the suspended active compound was made and the mass was wet-mixed to a proper consistency. The wet mass was pressed through an extruder and spheronized to pellets. The pellets were dried and classified into suitable particle size ranges.

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##### Subcoated pellets

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III	{	Uncoated pellets	500	g
		Hydroxypropyl methyl-cellulose	20	g
		Distilled water	400	g

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The polymer solution (III) was sprayed onto the uncoated pellets in a fluidized bed apparatus. The spray guns were placed above the fluidized bed.

## Enteric coated pellets

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IV	Subcoated pellets	500	g
	Hydroxypropyl methylcellulose		
	phthalate	57	g
	Cetyl alcohol	3	g
	Acetone	540	g
	Ethanol	231	g

20 The polymer solution (IV) was sprayed on the subcoated pellets in a fluidized bed apparatus with spray guns placed above the bed. After drying to a water content of 0.5 % the enteric coated pellets were classified and filled into hard gelatin capsules in an amount of 284 mg, corresponding to 25 mg of active compound 1. 30 capsules were packed in tight containers together with a desiccant.

## Example 2

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Formulation with the sodium salt of compound 2 according to Table I.

## Uncoated pellets

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I	Compound 2, Table I sodium salt	339	g
	Mannitol powder	2 422	g
	Lactose anhydrous	120	g
	Hydroxypropyl cellulose	90	g
	Microcrystalline cellulose	60	g
II	Sodium lauryl sulphate	7	g
	Distilled water	650	g

45

The preparation was made as described in Example 1 with the exception that the sodium salt of compound 2 was added together with the other ingredients in mixture I.

## Subcoated pellets

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		Uncoated pellets	500	g
5	III	{ Hydroxypropyl methylcellulose	20	g
		{ Aluminium hydroxide/magnesium carbonate	4	g
		{ Distilled water	400	g
10	IV	{ Pellets subcoated with III	500	g
		{ Hydroxypropyl methylcellulose	20	g
15		{ Distilled water	400	g

The two subcoat layers, III and IV, were applied to the uncoated pellets in a fluidized bed apparatus in consecutive order as previously described.

#### Enteric coated pellets

		Subcoated pellets	500	g
25	V	{ Hydroxypropyl methylcellulose		
		{ phthalate	57	g
		{ Cetyl alcohol	3	g
30		{ Acetone	540	g
		{ Ethanol	231	g

The preparation of enteric coated pellets was performed as described in Example 1.

#### Example 3

Formulation with compound 6, according to Table 1. This example gives the composition of one unit dose according to the invention.

#### Tablet core

Compound 6, Table 1	15 mg
Lactose	119 mg
Hydroxypropyl cellulose (low substitution)	5 mg
Hydroxypropyl cellulose	1 mg
Talc	5 mg
Mg(OH) <sub>2</sub>	15 mg
Total	160 mg

Tablet cores having the composition above and each weighing 160 mg were first made by known techniques.

#### Separating layer (inner)

Hydroxypropyl cellulose	2 mg
Synthetic hydrotalcite $[\text{Al}_2\text{O}_3 \cdot 6\text{MgO} \cdot \text{CO}_2 \cdot 12\text{H}_2\text{O}]$	0.3 mg

# Separating layer (outer)

Hydroxypropyl cellulose	2 mg
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The two separating layers were applied to the cores by known coating techniques.

# Enteric coating layer

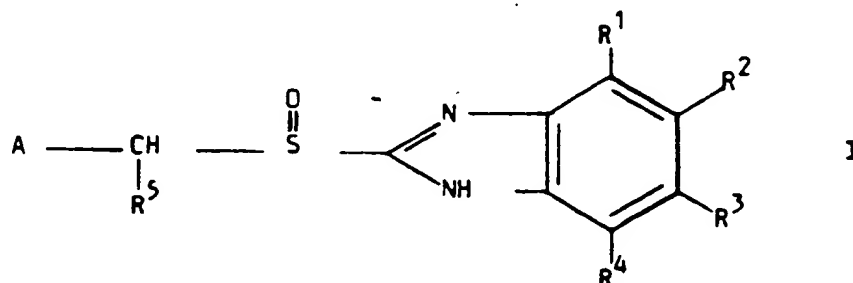
Hydroxypropyl methylcellulose phthalate	7 mg
Cetyl alcohol	0.5 mg

The enteric coating solution was sprayed on the cores coated by the two separating layers by known enteric coating techniques.

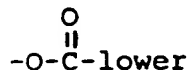
## **Claims**

Claims for the following Contracting States : BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. An oral, pharmaceutical preparation stable to discolouration containing an acid labile compound of the general formula I



wherein A is an optionally substituted heterocyclic group,  $\text{R}^1$ ,  $\text{R}^2$ ,  $\text{R}^3$  and  $\text{R}^4$  are the same or different and preferably hydrogen, lower alkyl, lower alkoxy,  $-\text{CF}_3$ ,



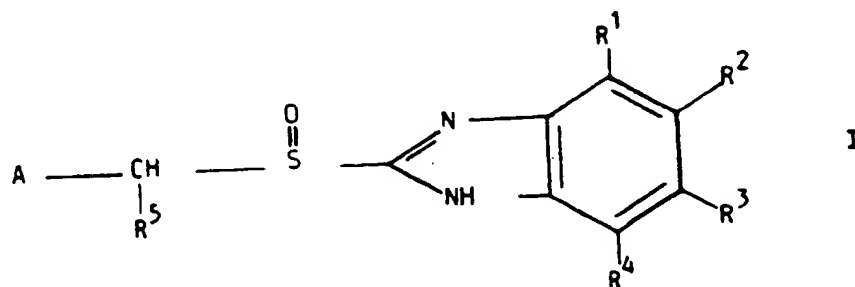
alkyl or halogen and  $\text{R}^5$  is H or a lower alkyl group wherein "lower" denotes 1-6 carbon atoms except the compound omeprazole, 5-methoxy-2-[(4-methoxy-3,5 dimethyl-2-pyridinyl) methyl] sulfinyl]-1H-benzimidazole; or the acid labile compound is 2-[(2-dimethylaminobenzyl)sulfinyl]-benzimidazole as the active ingredient characterized in that it is composed of core material in the form of small beads or tablets containing the active ingredient together with an alkaline reacting compound, or an alkaline salt of the active ingredient optionally together with an alkaline reacting compound, and on said core material one or more inert reacting subcoating layers comprising tablet excipients which are soluble or rapidly disintegrating in water, or polymeric, water soluble, filmforming compounds, optionally contain-

ing pH-buffering, alkaline compounds between the alkaline reacting core and an outer layer, which is an enteric coating.

2. A preparation according to claim 1 wherein the subcoating comprises hydroxypropyl methylcellulose, hydroxypropyl cellulose or polyvinylpyrrolidone.
3. A preparation according to claim 1 wherein the subcoating comprises two or more sub-layers and where the inner layer comprises one or more of magnesium oxide, magnesium hydroxide or composite substance  $\text{Al}_2\text{O}_3 \cdot 6\text{MgO} \cdot 2\text{SiO}_2 \cdot n\text{H}_2\text{O}$ , wherein n is not an integer and less than two.
4. A preparation according to claim 1 wherein the alkaline core comprises the acid labile compound and a pH-buffering alkaline compound rendering to the microenvironment of the acid labile compound a pH of 7-12.
5. A preparation according to claim 4 wherein the alkaline compound comprises one or more of magnesium oxide, hydroxide or carbonate, aluminium hydroxide, aluminium, calcium, sodium or potassium carbonate, phosphate or citrate, the composite aluminium/magnesium compounds  $\text{Al}_2\text{O}_3 \cdot 6\text{MgO} \cdot \text{CO}_2 \cdot 12\text{H}_2\text{O}$  or  $\text{MgO} \cdot \text{Al}_2\text{O}_3 \cdot 2\text{SiO}_2 \cdot n\text{H}_2\text{O}$ , wherein n not is an integer and less than two.
6. A preparation according to claim 1 wherein the alkaline core comprises an alkaline salt of the acid labile compound such as the sodium, potassium, magnesium, calcium or ammonium salt.
7. A preparation according to claim 5 wherein the alkaline core comprises an alkaline salt of the acid labile compound mixed with an alkaline otherwise inert compound.
8. A preparation according to claim 1 wherein the enteric coating comprises hydroxypropyl methylcellulose phthalate, cellulose acetate phthalate, co-polymerized methacrylic acid/methacrylic acid methyl ester or polyvinyl acetate phthalate, optionally containing a plasticizer.
9. A preparation according to claim 1 wherein the water content of the final dosage form containing the acid labile compound does not exceed 1.5 % by weight.
10. Process for the preparation of an oral pharmaceutical formulation stable to discolouration containing an acid labile compound according to claim 1 in which cores containing the acid labile compound mixed with an alkaline reacting compound or compounds or an alkaline salt of the acid labile compound optionally mixed with an alkaline reacting compound or compounds are coated with one or more inert reacting subcoating layers whereafter the subcoated cores are further coated with an enteric coating layer.

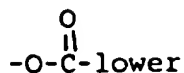
#### Claims for the following Contracting States : AT, ES, GR

1. A process for the preparation of an oral, pharmaceutical formulation stable to discolouration containing an acid labile compound of the general formula I



wherein A is an optionally substituted heterocyclic group,  $\text{R}^1$ ,  $\text{R}^2$ ,  $\text{R}^3$  and  $\text{R}^4$  are the same or different and preferably hydrogen,

lower alkyl, lower alkoxy, -CF<sub>3</sub>,



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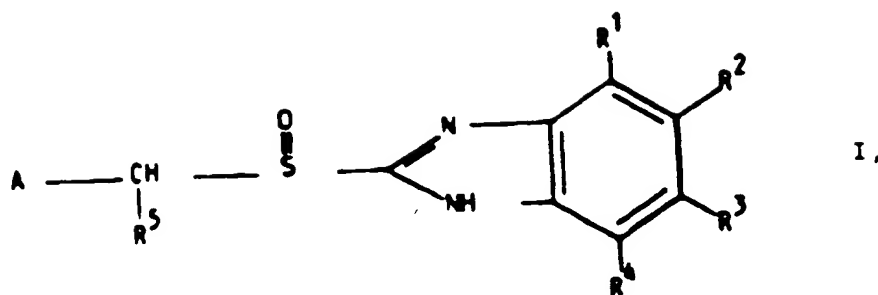
alkyl or halogen and R<sup>5</sup> is H or a lower alkyl group wherein "lower" denotes 1-6 carbon atoms except the compound omeprazole, 5-methoxy-2-[[[(methoxy-3,5 dimethyl-2-pyridinyl) methyl] sulfinyl]-1H-benzimidazole; or the acid labile compound is 2-[[[(2-dimethylamino) sulfinyl]-benzimidazole as the active ingredient characterized in that the acid labile compound mixed with an alkaline reacting compound, or an alkaline salt of the active ingredient optionally mixed with alkaline reacting compound, are formed to cores and said cores, which are in the form of small beads or tablets, are coated with one or more inert reacting subcoating layers comprising tablet excipients which are soluble or rapidly disintegrating in water, or polymeric, water soluble, filmforming compounds, optionally containing pH-buffering, alkaline compounds between the alkaline reacting core and an outer layer, which is an enteric coating layer, whereafter the subcoated cores are further coated with said outer enteric coating layer.

2. A process according to claim 1, wherein the applied subcoating comprises hydroxypropyl methylcellulose, hydroxypropyl cellulose or polyvinyl-pyrrolidone.
3. A process according to claim 1 wherein the applied subcoating comprises two or more sub-layers and where the inner sub-layer contains one or more of magnesium oxide, magnesium hydroxide or composite substance Al<sub>2</sub>O<sub>3</sub>.6MgO.CO<sub>2</sub>.12H<sub>2</sub>O or MgO.Al<sub>2</sub>O<sub>3</sub>.2SiO<sub>2</sub>.nH<sub>2</sub>O, wherein n not is an integer and less than two.
4. A process according to claim 1 wherein the acid labile compound is mixed with a pH-buffering alkaline compound rendering to the micro-environment of the acid labile compound a pH of 7-12, to form an alkaline core.
5. A process according to claim 4 wherein the alkaline compound which the acid labile compound is mixed with comprises one or more of magnesium oxide, hydroxide or carbonate, aluminium hydroxide, aluminium, calcium, sodium or potassium carbonate, phosphate or citrate, the composite aluminium/magnesium compounds Al<sub>2</sub>O<sub>3</sub>.6MgO.CO<sub>2</sub>.12H<sub>2</sub>O or MgO.Al<sub>2</sub>O<sub>3</sub>.2SiO<sub>2</sub>.nH<sub>2</sub>O wherein n not is an integer and less than two.
6. A process according to claim 1 wherein an alkaline salt of the acid labile compound such as the sodium, potassium, magnesium, calcium or ammonium salt is formed and incorporated into the alkaline core.
7. A process according to claim 6 wherein the alkaline core comprises an alkaline salt of the acid labile compound mixed with an alkaline otherwise inert compound.
8. A process according to claim 1 wherein the enteric coating which comprises hydroxypropyl methylcellulose phthalate, cellulose acetate phthalate, co-polymerized methacrylic acid/methacrylic acid methyl ester or polyvinyl acetate phthalate, optionally containing a plasticizer is applied.
9. A process according to claim 1 wherein a dosage form containing the acid labile compound is prepared in which the water content does not exceed 1.5 % by weight.

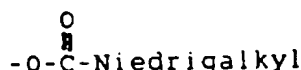
#### Patentansprüche

Patentansprüche für folgende Vertragsstaaten : BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. Orale pharmazeutische Präparation, die gegen Verfärbung stabil ist, welche Präparation eine säurelabile Verbindung der allgemeinen Formel I



15 worin A eine gegebenenfalls substituierte heterocyclische Gruppe ist, R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> und R<sup>4</sup> gleich oder verschieden und vorzugsweise Wasserstoff, Niedrigalkyl, Niedrigalkoxy, -CF<sub>3</sub>,



25 oder Halogen sind, und R<sub>5</sub> für H oder eine Niedrigalkylgruppe steht, worin "Niedrig" 1 bis 6 Kohlenstoffatome bezeichnet, mit Ausnahme der Verbindung Omeprazol, 5-Methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]-sulfinyl-1H-benzimidazol; oder die säurelabile Verbindung 2-[(2-Dimethylaminobenzyl)-sulfinyl]-benzimidazol als aktiven Inhaltsstoff umfaßt, dadurch gekennzeichnet, daß die Präparation aus Kernmaterial in Form von kleinen Kügelchen oder Tabletten, welches den

30 aktiven Inhaltsstoff zusammen mit einer alkalisch reagierenden Verbindung oder ein Alkalisalz des aktiven Inhaltsstoffes, gegebenenfalls zusammen mit einer alkalisch reagierenden Verbindung enthält, und einer oder mehreren inert reagierenden Basisüberzugsschichten auf dem Kernmaterial, umfassend in Wasser lösliche oder rasch zerfallende Tablettenhilfsstoffe oder polymere wasserlösliche filmbildende Verbindungen, die gegebenenfalls pH-puffernde Alkaliverbindungen zwischen dem alkalisch reagierenden Kern und einer äußeren Schicht, welche eine enterische Überzugsschicht ist, enthalten, zusammengesetzt ist.

- 35 2. Präparation nach Anspruch 1, worin der Basisüberzug Hydroxypropylmethylcellulose, Hydroxypropylcellulose oder Polyvinylpyrrolidon umfaßt.
- 40 3. Präparation nach Anspruch 1, worin der Basisüberzug zwei oder mehrere Unterschichten umfaßt, und wobei die innere Schicht eines oder mehrere von Magnesiumoxid, Magnesiumhydroxid oder der zusammengesetzten Substanz Al<sub>2</sub>O<sub>3</sub>.6MgO.CO<sub>2</sub>.12H<sub>2</sub>O oder MgO.Al<sub>2</sub>O<sub>3</sub>.2SiO<sub>2</sub>.nH<sub>2</sub>O, worin n keine ganze Zahl und weniger als 2 ist, umfaßt.
- 45 4. Präparation nach Anspruch 1, worin der alkalische Kern die säurelabile Verbindung und eine pH-puffernde Alkaliverbindung zur Herstellung einer Mikroumgebung der säurelabilen Verbindung von pH 7-12 umfaßt.
- 50 5. Präparation nach Anspruch 4, worin die Alkaliverbindung eines oder mehrere von Magnesiumoxid, -hydroxid oder -carbonat, Aluminiumhydroxid, Aluminium-, Calcium-, Natrium- oder Kaliumcarbonat, phosphat oder -citrat, der zusammengesetzten Aluminium/Magnesiumverbindungen Al<sub>2</sub>O<sub>3</sub>.6MgO.CO<sub>2</sub>.12H<sub>2</sub>O oder MgO.Al<sub>2</sub>O<sub>3</sub>.2SiO<sub>2</sub>.nH<sub>2</sub>O, worin n keine ganze Zahl und weniger als 2 ist, umfaßt.
- 55 6. Präparation nach Anspruch 1, worin der alkalische Kern ein Alkalisalz der säurelabilen Verbindung, wie das Natrium-, Kalium-, Magnesium-, Calcium- oder Ammoniumsalz umfaßt.
7. Präparation nach Anspruch 5, worin der alkalische Kern ein Alkalisalz der säurelabilen Verbindung in Mischung mit einer alkalischen, sonst inerten Verbindung umfaßt.
8. Präparation nach Anspruch 1, worin der enterische Überzug Hydroxypropylmethylcellulosephthalat,

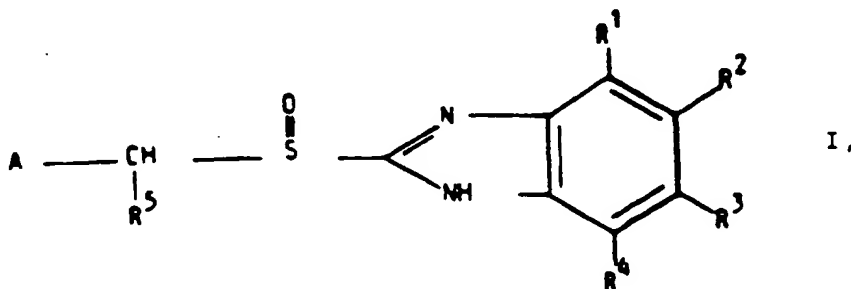
Celluloseacetatphthalat, copolymerisierten Methacrylsäure/Methacrylsäuremethylester oder Polyvinylacetatphthalat umfaßt und gegebenenfalls einen Weichmacher enthält.

9. Präparation nach Anspruch 1, worin der Wassergehalt der die säurelabile Verbindung enthaltenden endgültigen Dosisform 1,5 Gew.-% nicht übersteigt.

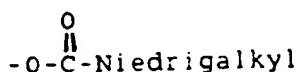
10. Verfahren zur Herstellung einer oralen pharmazeutischen Formulierung, die gegen Verfärbung stabil ist und eine säurelabile Verbindung nach Anspruch 1 enthält, in welcher Formulierung Kerne, enthaltend die säurelabile Verbindung in Mischung mit einer alkalisch reagierenden Verbindung oder Verbindungen oder ein Alkalisalz der säurelabilen Verbindung, gegebenenfalls gemischt mit einer alkalisch reagierenden Verbindung oder Verbindungen, mit einer oder mehreren inerten reagierenden Basisüberzugsschichten überzogen werden, wonach die mit dem Basisüberzug überzogenen Kerne weiters mit einer enterischen Überzugsschicht überzogen werden.

Patentansprüche für folgende Vertragsstaaten : AT, ES, GR

1. Verfahren zur Herstellung einer oralen pharmazeutischen Formulierung, die gegen Verfärbung stabil ist, welche Formulierung eine säurelabile Verbindung der allgemeinen Formel I



worin A eine gegebenenfalls substituierte heterocyclische Gruppe ist, R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> und R<sup>4</sup> gleich oder verschieden und vorzugsweise Wasserstoff, Niedrigalkyl, Niedrigalkoxy, -CF<sub>3</sub>,



oder Halogen sind, und R<sub>5</sub> für H oder eine Niedrigalkylgruppe steht, worin "Niedrig" 1 bis 6 Kohlenstoffatome bezeichnet, mit Ausnahme der Verbindung Omeprazol, 5-Methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridinyl]-methyl]-sulfinyl]-1H-benzimidazol; oder die säurelabile Verbindung 2-[(2-Dimethylaminobenzyl)-sulfinyl]-benzimidazol als aktiven Inhaltsstoff enthält, dadurch gekennzeichnet, daß die säurelabile Verbindung in Mischung mit einer alkalisch reagierenden Verbindung oder ein Alkalisalz des aktiven Inhaltsstoffes, gegebenenfalls gemischt mit einer alkalisch reagierenden Verbindung, zu Kernen geformt werden, und die Kerne, welche die Form von kleinen Kügelchen oder Tabletten aufweisen, mit einer oder mehreren inert reagierenden Basisüberzugsschichten, umfassend in Wasser lösliche oder rasch zerfallende Tablettenhilfsstoffe oder polymere wasserlösliche filmbildende Verbindungen, die gegebenenfalls pH-puffernde Alkaliverbindungen zwischen dem alkalisch reagierenden Kern und einer äußeren Schicht, welche eine enterische Überzugsschicht ist, enthalten, überzogen werden, worauf die mit dem Basisüberzug überzogenen Kerne weiters mit der äußeren enterischen Überzugsschicht überzogen werden.

2. Verfahren nach Anspruch 1, worin der aufgebrauchte Basisüberzug Hydroxypropylmethylcellulose, Hydroxypropylcellulose oder Polyvinylpyrrolidon umfaßt.
3. Verfahren nach Anspruch 1, worin der aufgebrauchte Basisüberzug zwei oder mehrere Unterschichten umfaßt, und wobei die innere Unterschicht eines oder mehrere von Magnesiumoxid, Magnesiumhydro-

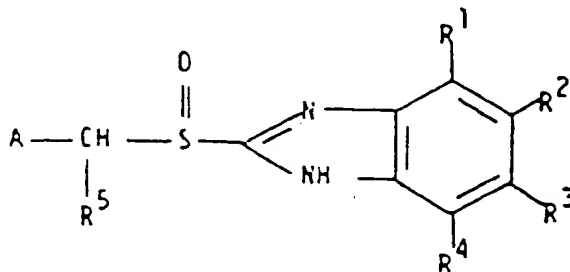
xid oder der zusammengesetzten Substanz  $\text{Al}_2\text{O}_3 \cdot 6\text{MgO} \cdot \text{CO}_2 \cdot 12\text{H}_2\text{O}$  oder  $\text{MgO} \cdot \text{Al}_2\text{O}_3 \cdot 2\text{SiO}_2 \cdot n\text{H}_2\text{O}$ , worin n keine ganze Zahl und weniger als 2 ist, umfaßt.

4. Verfahren nach Anspruch 1, worin die säurelabile Verbindung mit einer pH-puffernden Alkaliverbindung zur Herstellung einer Mikroumgebung der säurelabilen Verbindung von pH 7-12 gemischt ist, wobei ein alkalischer Kern gebildet wird.
5. Verfahren nach Anspruch 4, worin die Alkaliverbindung mit welcher die säurelabile Verbindung in Mischung ist, eines oder mehrere von Magnesiumoxid, -hydroxid oder -carbonat, Aluminiumhydroxid, Aluminium-, Calcium-, Natrium- oder Kaliumcarbonat, -phosphat oder -citrat, der zusammengesetzten Aluminium/Magnesiumverbindungen  $\text{Al}_2\text{O}_3 \cdot 6\text{MgO} \cdot \text{CO}_2 \cdot 12\text{H}_2\text{O}$  oder  $\text{MgO} \cdot \text{Al}_2\text{O}_3 \cdot 2\text{SiO}_2 \cdot n\text{H}_2\text{O}$ , worin n keine ganze Zahl und weniger als 2 ist, umfaßt.
6. Verfahren nach Anspruch 1, worin ein Alkalisalz der säurelabilen Verbindung, wie das Natrium-, Kalium-, Magnesium-, Calcium- oder Ammoniumsalz, gebildet wird und in den alkalischen Kern inkorporiert wird.
7. Verfahren nach Anspruch 6, worin der alkalische Kern ein Alkalisalz der säurelabilen Verbindung in Mischung mit einer alkalischen, sonst inerten Verbindung umfaßt.
8. Verfahren nach Anspruch 1, worin der enterische Überzug, welcher Hydroxypropylmethylcellulosephthalat, Celluloseacetatphthalat, copolymerisierten Methacrylsäure/Methacrylsäuremethylester oder Polyvinylacetatphthalat umfaßt und gegebenenfalls einen Weichmacher enthält, angewandt wird.
9. Verfahren nach Anspruch 1, worin eine die säurelabile Verbindung enthaltende Dosisform hergestellt wird, wobei ihr Wassergehalt 1,5 Gew.-% nicht übersteigt.

#### Revendications

Revendications pour les Etats contractants suivants : BE, CH, DE, FR, GB, IT, LI, LU, NL, SE,

1. Préparation pharmaceutique orale résistant à la décoloration contenant un composé sensible aux acides de formule générale I :



dans laquelle A est un groupe hétérocyclique éventuellement substitué,  $R^1$ ,  $R^2$ ,  $R^3$  et  $R^4$  sont identiques ou différents et sont de préférence des atomes d'hydrogène, des groupes alkyle inférieurs, alcoxy inférieurs  $-\text{CF}_3$ ,



inférieur ou halogène et  $R^5$  est un atome d'hydrogène ou un groupe alkyle inférieur, où "inférieur" signifie de 1 à 6 atomes de carbone, exception faite du composé oméprazole, 5-méthoxy-2-[[4-méthoxy-3,5-diméthyl-2-pyridinyl)méthyl]sulfanyl]-1H-benzimidazole ; ou bien le composé sensible aux acides est le 2-[(2-diméthylaminobenzyl)sulfanyl]benzimidazole, comme ingrédient actif, caractérisée

en ce que' elle est composée d'une substance de noyau sous la forme de petites perles ou de comprimés contenant l'ingrédient actif ainsi qu'un composé à réaction alcaline , ou un sel alcalin de l'ingrédient actif ainsi éventuellement qu'un composé à réaction alcaline, et , sur ladite substance de noyau, d'une ou plusieurs couches de sous-enrobage inertes comprenant des excipients pour comprimés qui sont solubles ou qui se désintègrent rapidement dans l'eau, ou des composés filmogènes polymères hydrosolubles, contenant éventuellement des composés alcalins servant de tampon de pH entre le noyau à réaction alcaline et une couche externe , qui est un enrobage à délitement entérique .

2. Préparation selon la revendication 1, dans laquelle le sous-enrobage comprend de l'hydroxypropylméthylcellulose , de l'hydroxypropylcellulose ou de la polyvinylpyrrolidone .

3. Préparation selon la revendication 1, dans laquelle le sous-enrobage comprend deux ou plusieurs sous-couches et dans laquelle la couche intérieure comprend une ou plusieurs substances parmi l'oxyde de magnésium, l'hydroxyde de magnésium ou une substance composite  $Al_2O_3, 6MgO, CO_2, 12H_2O$  ou  $MgO, Al_2O_3, 2SiO_2, nH_2O$ , où n n'est pas un nombre entier et est inférieur à 2.

4. Préparation selon la revendication 1, dans laquelle le noyau alcalin comprend le composé sensible aux acides et un composé alcalin servant de tampon de pH conférant au micro-environnement du composé sensible aux acides un pH de 7-12.

5. Préparation selon la revendication 4, dans laquelle le composé alcalin comprend une ou plusieurs substances parmi l'oxyde, l'hydroxyde ou le carbonate de magnésium, l'hydroxyde d'aluminium, le carbonate , le phosphate ou le citrate d'aluminium, de calcium, de sodium ou de potassium, les composés composites aluminium/magnésium  $Al_2O_3, 6MgO, CO_2, 12H_2O$  ou  $MgO, Al_2O_3, 2SiO_2, nH_2O$ , où n n'est pas un nombre entier et est inférieur à 2.

6. Préparation selon la revendication 1, dans laquelle le noyau alcalin comprend un sel alcalin du composé sensible aux acides comme le sel de sodium, de potassium, de magnésium, de calcium ou d'ammonium.

7. Préparation selon la revendication 5, dans laquelle le noyau alcalin comprend un sel alcalin du composé sensible aux acides mélangé avec un composé alcalin inerte par ailleurs.

8. Préparation selon la revendication 1, dans laquelle l'enrobage à délitement entérique comprend du phtalate d'hydroxypropylméthylcellulose, de l'acétate-phtalate de cellulose, un copolymère d'acide méthacrylique et d'ester méthylique d'acide méthacrylique ou du poly(acétate-phtalate de vinyle), contenant éventuellement un plastifiant.

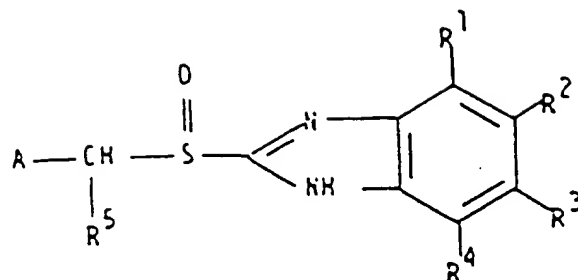
9. Préparation selon la revendication 1, dans laquelle la teneur en eau de la forme posologique finale contenant le composé sensible aux acides ne dépasse pas 1,5% en poids .

10. Procédé de préparation d'une formulation pharmaceutique orale résistante à la décoloration contenant un composé sensible aux acides selon la revendication 1 dans lequel les noyaux contenant le composé sensible aux acides mélangé avec un composé ou des composés à réaction alcaline ou un sel alcalin du composé sensible aux acides éventuellement mélangé avec un composé ou des composés à réaction alcaline sont enrobés avec une ou plusieurs couches de sous-enrobage inertes, puis les noyaux sous-enrobés sont ensuite enrobés d'un enrobage à délitement entérique.

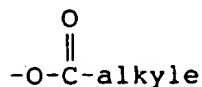
#### Revendications pour les Etats contractants suivants : AT, ES, GR

1. Procédé de préparation d'une formulation pharmaceutique orale résistante à la décoloration contenant un composé sensible aux acides de formule générale I :





dans laquelle A est un groupe hétérocyclique éventuellement substitué, R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> et R<sup>4</sup> sont identiques ou différents et sont de préférence des atomes d'hydrogène, des groupes alkyle inférieurs, alcoxy inférieurs, -CF<sub>3</sub>-,



inférieur ou halogène et R<sup>5</sup> est un atome d'hydrogène ou un groupe alkyle inférieur, où "inférieur" signifie de 1 à 6 atomes de carbone, exception faite du composé oméprazole, 5-méthoxy-2-[(méthoxy-3,5-diméthyl-2-pyridinyl)méthylsulfanyl]-1H-benzimidazole ; ou bien le composé sensible aux acides est le 2-[(2-diméthylaminobenzyl)sulfanyl]benzimidazole, comme ingrédient actif, caractérisé en ce que l'on met sous forme de noyaux le composé sensible aux acides mélangé avec un composé à réaction alcaline, ces noyaux, qui se présentent sous la forme de petites perles ou de comprimés, sont enrobés d'une ou plusieurs couches de sous-enrobage inertes comprenant des excipients pour comprimés qui sont solubles ou qui se désintègrent rapidement dans l'eau, ou des composés filmogènes polymères hydrosolubles, contenant éventuellement des composés alcalins servant de tampon de pH entre le noyau à réaction alcaline et une couche externe, qui est un enrobage à délitement entérique, puis les noyaux sous-enrobés sont ensuite enrobés de ladite couche d'enrobage externe à délitement entérique.

2. Procédé selon la revendication 1, dans lequel le sousenrobage appliqué comprend de l'hydroxypropyl-méthylcellulose, de l'hydroxypropylcellulose ou de la polyvinyl-pyrrolidone.
3. Procédé selon la revendication 1, dans lequel le sousenrobage appliqué comprend deux ou plusieurs sous-couches et dans lequel la sous-couche intérieure contient une ou plusieurs substances parmi l'oxyde de magnésium, l'hydroxyde de magnésium ou une substance composite Al<sub>2</sub>O<sub>3</sub>.6MgO, CO<sub>2</sub>, 12H<sub>2</sub>O ou MgO, Al<sub>2</sub>O<sub>3</sub>, 2SiO<sub>2</sub>, nH<sub>2</sub>O, où n n'est pas un nombre entier et est inférieur à deux.
4. Procédé selon la revendication 1, dans lequel le composé sensible aux acides est mélangé avec un composé alcalin servant de tampon de pH conférant au micro-environnement du composé sensible aux acides un pH de 7-12, pour former un noyau alcalin.
5. Procédé selon la revendication 4, dans lequel le composé alcalin avec lequel est mélangé le composé sensible aux acides comprend une ou plusieurs substances parmi l'oxyde, l'hydroxyde ou le carbonate de magnésium, l'hydroxyde d'aluminium, le carbonate, le phosphate ou le citrate d'aluminium, les composés composites d'aluminium et de magnésium Al<sub>2</sub>O<sub>3</sub>, 6MgO, CO<sub>2</sub>, 12H<sub>2</sub>O ou MgO, Al<sub>2</sub>O<sub>3</sub>, 2SiO<sub>2</sub>, nH<sub>2</sub>O, où n n'est pas un nombre entier et est inférieur à deux.
6. Procédé selon la revendication 1, dans lequel le sel alcalin du composé sensible aux acides, tel que le sel de sodium, de potassium, de magnésium, de calcium ou d'ammonium, est formé et incorporé dans le noyau alcalin.
7. Procédé selon la revendication 6, dans lequel le noyau alcalin comprend un sel alcalin du composé sensible aux acides mélangé avec un autre composé alcalin inerte par ailleurs.

8. Procédé selon la revendication 1, dans lequel on applique l'enrobage à délitement entérique qui comprend du phtalate d'hydroxypropylméthylcellulose, de l'acétate-phtalate de cellulose, un copolymère d'acide méthacrylique et d'ester méthylique d'acide méthacrylique ou du poly(acétatephtalate de vinyle), contenant éventuellement un plastifiant.

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9. Procédé selon la revendication 1, dans lequel on prépare une forme posologique contenant le composé sensible aux acides dans lequel la teneur en eau ne dépasse pas 1,5% en poids.

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